IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicant(s): Stavrianopoulos et al.
Serial No. 08/486,070 Group Art Unit: 1631
Filed: June 7, 1995 Examiner: Ardin H. Marschel, Ph.D.
Title: **SOLID SUPPORT COMPRISING AN ARRAY OF SUBSTRATE SURFACES FOR NUCLEIC ACID ANALYSES AND APPLICATIONS, AND OTHER COMPOSITIONS AND SYSTEMS EMPLOYING CHEMICALLY LABELED OLIGONUCLEOTIDES OR POLYNUCLEOTIDES**
(As Previously Amended)

FILED BY EXPRESS MAIL

Honorable Commissioner of
Patents and Trademarks
Washington, D. C. 20231

Sir:

Transmitted herewith is a Communication For Transmitting Declaration Of Cheryl H. Agris, Ph.D., Attorney At Law (Following Applicants' April 26, 2001 Communication) in the above-identified patent application.

The fee has been calculated as shown below:

	CLAIMS REMAINING AFTER AMENDMENT		HIGHEST NUMBER PREVIOUSLY PAID FOR	PRESENT EXTRA	RATE	ADDITIONAL FEE
Total	828	Minus	828	= 0	X $ 18	$ 0
Indep	11	Minus	11	= 0	X $ 80	$ 0
( )	First Presentation of Multiple Dependent Claims				+$270	$ 0
	TOTAL ADDITIONAL FEE					$ 0

( ) Charge Deposit Account No. 05-1135 in the amount of $_____.
( ) A check in the amount of $_____ is attached.
(X) The Commissioner is hereby authorized to charge payment of the following fees associated with this communication or credit any overpayment to Deposit Account No. 05-1135: any filing fees under 37 C.F.R. §1.16 for the presentation of extra claims and any patent application processing fees under 37 C.F.R. §1.17.

Copies are being provided in triplicate.

Also enclosed: _____

Respectfully submitted,

May 8, 2001
Date

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EXPRESS MAIL CERTIFICATE

"Express Mail" Label No. EL705916858US
Deposit Date May 8, 2001
I hereby certify that this paper and the attachments herein are being deposited with the United States Postal Service "Express Mail Post Office to Addressee" service under 37 CFR 1.10 on the date indicated above and is addressed to the Commissioner of Patents and Trademarks, Washington DC 20231.

Ronald C. Fedus
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MAY 8 2001
Date

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#34 Plunkett 5/30/10

Group Art Unit: 1631

Ex'r: Ardin H. Marschel, Ph.D.

527 Madison Avenue (9th Floor)
New York, New York 10022

May 8, 2001

FILED BY EXPRESS MAIL

Honorable Commissioner of Patents and Trademarks
Washington, D.C. 20231

COMMUNICATION FOR TRANSMITTING DECLARATION OF CHERYL H. AGRIS, Ph.D., ATTORNEY AT LAW (FOLLOWING APPLICANTS' APRIL 26, 2001 COMMUNICATION)

Dear Sirs:

This Communication follows Applicants' April 26, 2001 Communication For Transmitting Composite Claim Set and it also follows their March 7, 2001 Amendment Under 37 C.F.R. §1.115, the latter having been filed in response to the September 7, 2000 Office Action issued in connection with their above-identified application. No extension request or extension fee is believed due in connection with this filing, a Request For An Extension Of Time (3 Months) and authorization for the fee therefor having been previously submitted with Applicants' March 7, 2001 Amendment.

EXPRESS MAIL CERTIFICATE

"Express Mail" Label No. EL705916858USUS
Deposit Date May 8, 2001
I hereby certify that this paper and the attachments herein are being deposited with the United States Postal Service "Express Mail Post Office to Addressee" service under 37 CFR 1.10 on the date indicated above and is addressed to the Commissioner of Patents and Trademarks, Washington DC 20231.

Ronald C. Fedus
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MAY 8 2001
Date

pages 7-8 of the instant specification. Consideration of this page 7-8 citation reveals that it was cited as a reference which reviewed non-radioactive signalling and bridging/signalling systems. It was not cited for any other disclosure. This is an incorporation by reference of pointed to subject matter but not other subject matter. Such incorporations by reference must be directed to particular disclosures for them to be usable for giving written basis for claim limitations.. A specific claim limitation is clearly essential subject matter. It is improper to incorporation by reference essential subject matter cited in a foreign patent application. It is improper to generically cite such a reference and then utilize it for anything therein without defining in the citation what it is cited for. In this case the publication was cited for non-radioactive signalling etc. review and not for mutation types. Thus, it does not serve as a proper basis for incorporating mutation types into the instant claims. For further discussion, see the M.P.E.P. at section 608.01(p), part I, subsection A. The following claims contain this NEW MATTER: 206, 246, 294, 349, 375, 376, 424, 464, 512, 583, 622, and 669.

[7] Several of the instant claims contain the limitation given as "partially double-stranded". This limitation is NEW MATTER in that the limitation has not been found as filed. In the amendment, filed 5/19/99, Examples 1-7 were cited for support. Consideration of said Examples 1-7 has failed to reveal written basis for this limitation. The following claims contain this NEW MATTER: 207, 247, 295, 345, 375, 376, 425, 465, 513, 584, 623, and 670.

[8] Several of the instant claims contain the limitation given as "aminopropyltriethoxysilane". This limitation is NEW MATTER in that the closest limitation as filed is given as the more limited material: gamma-aminopropyltriethoxysilane. This material is cited in the instant specification on page 15, lines 26-27. The added breadth of this material without also being of the "gamma" type is NEW MATTER. The following claims contain this NEW MATTER: 328, 375, 376, 379, 387, 395, 539, 547, 555, 696, 704, and 712.

[9] Several of the instant claims contain the limitation given as "a dispersive compound". This limitation is NEW MATTER because this broad concept of a dispersive compound has not been found as filed. The following claims contain this NEW MATTER: 330, 331, 375, 376, 381, 382, 389, 390, 397, 398, 541, 542, 549, 550, 557, 558, 698, 699, 706, 707, 714, and 715.

The new matter rejection is respectfully traversed.

In order to address each and every point raised in the new matter rejection above, Applicants' attorney has inserted bold bracketed numbers. The remarks below are directed to those points designated by the bold bracketed numbers.

[1] With respect to the array issue, it is important to note that new claims 718-872 are all directed to a solid support comprising an array of substrate surfaces. The fixation or immobilization of nucleic acid to a solid support, including

the aforementioned array of substrate surfaces, is an inventive concept universally disclosed throughout Applicants' original specification. Applicants' invention has spawned innumerable useful applications in nucleic acid technology, including detection, genetic and sequence analysis, and drug screening. Applicants' inventive concept can be best understood by viewing two charts which have been prepared from the specification at hand. Attached as Exhibit 2, the first chart shows the interrelationship between the solid support and various other elements or embodiments, including nature of the support material, surface treatments, devices, apparatus and, of course, the array subject matter. List on the second chart which is attached as Exhibit 3, are citations to the specification which support the various elements, embodiments and relationships.

At the outset, it must be kept in mind that the above-quoted statement in the new matter rejection (page 16, lines 9-27) is only a *part* of Example 1 (specification, pages 15-16), and this is an example which uses a "glass support" and a borosilicate "glass surface," neither of which embodiment has "wells or depressions."

The statement immediately preceding Example 1 on page 15 in the specification states:

> DETAILED DESCRIPTION
>
> The following examples are illustrative of preferred embodiments of the method of the present invention. Specifically referred to therein are methods for fixing the analyte to a **non-porous solid support**, as well as illustrations of the use of soluble signals in polynucleotide probes as discussed above.

The rest of the examples (2-7) disclose a number of different forms of the non-porous solid support stated above, including:

Example 2: **glass surface** of Example 1
Example 3: activated **glass surface (glass tubes)**
Example 5: **plastic surface**
plastic plates
Example 6: **polystyrene plates**
non-porous siliceous solid support,
such as **glass** and **plastic**
Example 7: conventional **microtiter well plates**

The passage cited in th new matter rejection (page 16, lines 9-27) begins with the introductory phrase "***For example, . . .***" Thus, the use of glass plates (or plastic plates which the Examiner is willing to allow) with wells or depressions is but an example of the claimed array.

Significantly, other portions in the specification disclose the array subject matter *without limitation* to "wells or depressions." To begin with, the specification quite clearly and significantly *equates* "device" with "solid support" in the first paragraph on page 14:

> . . . ***It may also be desirable for*** both the solid support to which the analyte is fixed and the device to be composed of the same material, or for ***the device to function as the support*** in addition to facilitating spectrophotometric detection.

"Devices" are also described later in the second paragraph on page 14:

> . . . A related product of the invention is an apparatus comprising a **plurality of such devices** for containing a fluid, **in which at least one such device contains the above-described immobilized polynucleotide sequence**, polynucleotide or oligonucleotide probe, signalling moiety, and soluble signal.

The devices referenced above in page 14, first paragraph, are further described variously in the specification. For example, beginning with the last four lines on page 13, and continuing through the first line on page 14 in the specification, it is disclosed:

> . . . ***Examples of devices*** useful in the spectrophotometric analysis of the signal include ***conventional apparatus*** employed in diagnostic laboratories, i.e., plastic or glass wells, tubes, cuvettes or arrangements of wells, tubes or cuvettes.

Continuing on page 14, lines 19-20, it is also disclosed:

> . . . The ***portion of the device for containing the fluid*** is desirably a ***well, a tube, or a cuvette***.

Other description for the "device" is found in originally filed claim 17 from the original specification:

> Claim 17. The method in accordance with Claim 16, characterized in that said ***device*** is selected from the group consisting of ***a well, a tube, a cuvette and an apparatus which comprises a plurality of said wells, tubes or cuvettes***.

"Means for containing a fluid" is also defined by originally filed claim 23 in the specification:

Claim 23 An apparatus comprising:

a plurality of means for containing a fluid, wherein at least one of said means comprises:

(i) an ***immobilized polynucleotide sequence hybridized to a polynucleotide or oligonucleotide probe***, said probe having covalently attached thereto a chemical label comprising a signalling moiety capable of forming a soluble signal, and

(ii) a soluble signal generated by means of said signalling moiety.

Furthermore, the above-recited means for containing a fluid is also found in originally filed claim 21 from the specification:

Claim 21. The ***device*** according to Claim 20, wherein said ***means for containing a fluid*** is selected from the group consisting of ***a well, a tube, and a cuvette***.

It should not be overlooked that the portion in the disclosure cited in the new matter rejection refers to "the single-stranded analytes being fixed to the ***surfaces*** of the wells." Just as in the case of any non-porous solid support, or any device, or any means for containing a fluid, or any well or depression, or any tube or cuvette, it is ultimately the ***surface of such support*** (or device, means for containing a fluid, well or depression, tube or cuvette) to which the oligo- or polynucleotides are fixed or immobilized. The fact that the oligo- or polynucleotides are fixed or immobilized to the surfaces of such elements is seen in several instances in the specification:

a) Example 2

"A ***glass surface*** as described in Example 1 can be employed . . .

b) Example 3

. . . In these tests, the analyte, phage lambda DNA, was immobilized on an activated ***glass surface*** . . .

c) Example 5

The advantages of the practices of this invention are also obtainable when the probe is immobilized on a ***non-porous plastic surface***. When a ***plastic surface*** is employed, it is sometimes desirable to increase the effectiveness or uniformity of the fixation by pretreating the ***plastic surface***.

Because polystyrene from various batches or sources exhibits different binding capacities, the adherence or fixing of DNA to a ***polystyrene surface*** is improved by ***treating the surface*** with an amino-substituted hydrophobic polymer or material. . . Another

technique for improving the fixing or uniformity of the ***plastic surface*** for fixing DNA involves ***treatment of the surface*** with polylysine (PL).

In tests involving the fixing the DNA to a ***plastic surface***, biotinylated DNA (bDNA) was denatured and aliquoted into Dynatech, Immulon II™ removeable wells.

d) Example 6

An improved capability for fixing or immobilization of DNA to non-porous siliceous solid supports, such as glass and plastic, is also provided by treatment with a coating of an epoxy resin. For example, ***treatment of glass or polystyrene surfaces*** with commercially available epoxy glues, such as a solution of epoxy glue in ethanol [1 percent w/v] serves this purpose. These epoxy solutions are applied to the ***surfaces or wells***, and the solvent, ethanol, evaporated thereon at a temperature of 37° C, thereby providing a polyamine polymeric coating on the ***treated surface***. These ***surfaces*** were found to absorb ^{3}H-labeled DNA from aqueous solution at pH less than 9.5.

It is quite clear and even beyond dispute that Applicants' disclosure covering their claimed solid supports comprising an array of substrate surfaces" extends far beyond the one quoted passage (page 16, lines 9-27).

On the issue of the omitted essential element, the case law fully supports Applicants' claimed array subject matter. As described above, the present specification describes the claimed array without limitation to "wells or depressions." Generally, the test for the "omitted essential element" is whether or not a person skilled in the art would have understood the element(s) to be essential to the disclosed invention. In this case, properly phrased, the test for the "omitted essential element" is whether a person skilled in the art would have understood "wells or depressions" to be essential elements of our claimed array. The omitted essential element rule cannot be applied to the present case and claims which can be wholly distinguished from *Gentry*, the leading case and controlling authority on the doctrine.

1. In the *Gentry* case [Gentry Gallery, Inc. v. Berkline Corporation, 134 F.3d 1473 (Fed. Cir. 1998), 45 USPQ2d 1498 (Fed. Cir. 1998)], the issue was whether the placement of controls on a console in a reclining sofa was an *essential* element of the invention in the original application. A copy of the *Gentry* case is

attached as Exhibit 4. After reviewing the Objects of the Invention, the scope of the claims submitted with the original application and other descriptions in the specification, the Court ruled that the location of the recliner control on the console was an "essential element" of the described invention. [134 F.3d at 1479, 45 USPQ2d at 1503]. The Court reached this conclusion because no other disclosure could be found in the original application for placing the controls on a console in a *different* position on the sofa. In other words, "the inventor did not have an alternate location in mind when he made his initial disclosure," to borrow from the *Reiffin* case, discussed *infra*. Here, as described above, wells or depressions are not defined to be essential elements of the claimed array because

- the example itself (Example 1, pages 15-16) is drawn to a "***glass surface***" and a "***borosilicate glass surface***"
- All of the examples (1-7) are stated to be illustrative of preferred embodiments . . . and method for ***fixing*** . . . ***to a non-porous solid support***.
- The passage cited in the new matter rejection (page 16, lines 9-27) begins with the introductory phrase "***For example***, . . .
- Arrays are disclosed in other portions of the specification without limitation to "wells or depressions," including a ***plurality of devices for containing a fluid***" and "a ***plurality of means for containing a fluid***."
- Devices, including the array device (an ***apparatus comprising a plurality of devices for containing a fluid***, page 14, lines 21-26) are likewise not limited to "wells or depressions."
- Moreover, ***any device in this invention can function as a*** [non-porous] ***solid support***, as well as be composed of the same material.

2. In the *Reiffin* case [Reiffin v. Microsoft Corp., 48 USPQ2d 1274 (N.D. Calif. 1998), another case involving an issue of the omitted essential element, summary judgment for the defendant was granted and the plaintiff's patent was invalidated based on the omission of four elements deemed to be essential to describe the plaintiff's patented invention for a "multithreading" computer technology. In that case which cited the *Gentry* case prominently, the California District Court examined the "Summary of the Invention," the abstract, the "Object of the Invention," the "Description of Prior Art," and the originally filed claims,

before ruling that essential elements had been omitted from the issued claims. The Court also noted that at least one of the four elements was referenced in each of the patent's 21 original claims. A copy of the *Reiffin* case is attached as Exhibit 5.

In summary, the specification does not limit the claimed array to "wells or depressions," even in the disclosure (page 16, lines 9-27) cited in the rejection which is only given as an "example." Other disclosure is provided in the specification where solid supports comprising an array of substrate surfaces are described as devices or means for containing a fluid, and such devices or means are not limited to wells or depressions, but can include tubes or cuvettes, or arrangements of wells, tubes or cuvettes. More importantly, devices are specifically stated to "function as the [solid] support" (page 14, lines 1-5), and as set forth in the support charts (Exhibits 2 and 3), the surfaces used in the solid supports can take many forms and can be made from many different kinds of materials. Further, these materials can be treated in many ways to facilitate fixation or immobilization of nucleic acid thereon. Moreover, it is the surface of the solid support (or device or array or apparatus or means for containing a fluid or even the "wells or depressions") to which the oligo- or polynucleotides are ultimately being fixed or immobilized. The presence or absence of "wells or depressions" is immaterial to the present invention and claims whereby oligo- or polynucleotides have been fixed or immobilized to the surfaces of non-porous solid supports.

[2] The broader term "cellulose" has been expunged from the new claims which recite "nitrocellulose" in various dependent claims.

[3] [4] It is believed that the use of the terms "glass-coated" and "plastic-coated" is adequately described in the specification. It is equally reasonable to interpret the claims containing these terms to mean that the surface has been treated with an agent. As described in **[1]** above with respect to the array issue, several portions and examples in the specification relate to coating glass or plastic surfaces. See Examples 1-2 and 4-6. In the first paragraph of Example 3, it is stated that "glass tubes were coated with 100 µl of coating solution [50 percent formamide, 5X SSC, 100 µg salmon sperm DNA, 0.2 percent polyvinylpyrrolidone, 0.1 percent Triton X-100, 0.2 percent BSA and 0.05 percent SDS] at 42° C for 90-120 minutes." In Example 6, page 22, last paragraph, it is disclosed that "[a]n